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(54) Title: FORMULATION COMPRISING MICROPARTICLES, FOR INHALATION

(57) Abstract

Microparticles, up to 50 μm in size, comprising a therapeutic agent and a surfactant. They can be homogeneously formulated with a HFC propellant.

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FORMULATION COMPRISING MICROPARTICLES, FOR INHALATION

Field of the Invention

This invention relates to a formulation of a drug, in the form of microparticles, suitable for administration by means of a metered dose inhaler.

Background of the Invention

Drugs to be administered to the airways may be formulated dry, for use in a dry powder inhaler, or in a solution or suspension, to be delivered by means of a pressurised metered dose inhaler (pMDI). Suspensions/ formulations of pMDIs typically comprise the drug, micronised to a respirable particle size, surfactant such as oleic acid, lecithin or Span®85, and a propellant. In the past, the propellant has been a chlorofluorocarbon (CFC) such as P11, P12 or P114. CFCs are good solvents for surfactants, but their use involves major environmental concerns. Suitable replacement propellants include the hydrofluoroalkanes HFA134a and HFA227, but the solubility of surfactants in HFAs is poor, and this is reflected in the resulting suspension characteristics.

The solubility of the surfactant in HFAs has been increased by the use of saturated hydrocarbons and alcohols, e.g. ethanol, as disclosed in EP-A-0372777. Alternatively, the surfactant may be adsorbed onto the drug particle surface. However, the surfactant may have limited solubility in the propellant and, in the case of suspension metered dose inhalers, it is then difficult to achieve sufficient adsorption of surfactant onto the drug particle surface to facilitate a controlled flocculation system which is stable.

An object behind the present invention is to avoid the disadvantages of poor surfactant solubility and consequent drug suspension instability described above.

Summary of the Invention

It has now been realised that spray-drying is useful as a means to produce novel drug particles of respirable size range, containing surfactant. This can provide high

local concentrations of surfactant on the surface of the particle, to create the appropriate repulsive forces between particles. More particularly, by balancing the repulsive forces through formulation (i.e. quantity and type of surfactant, pH, etc), when particles are attracted by Van der Waals forces, they are unable to move close together because of electrostatic, steric and entropic repulsive forces. In these circumstances, floccules are formed. The sediment will have a large volume and, because the balancing attractive force is relatively weak, the floccules are easily dispersed.

Microparticles according to this invention comprise a therapeutic agent and a surfactant. The use of spray-drying can provide a product in which the surfactant is uniformly distributed through the matrix of drug and, if necessary or desired, a wall-forming excipient. The microparticles can be formulated with a propellant, e.g. a HFA, for use in a metered dose inhaler.

Description of the Invention

The components used in this invention may all be conventional. Drugs for use in therapy, administered by inhalers, are exemplified in WO-A-9608914. Suitable surfactants include oleic acid, lecithin and sorbitan trioleate as are used in conventional metered dose inhalers. A fuller list of types and examples of suitable surfactants is given in EP-A-0372777, which also describes relevant drugs.

Spray-drying techniques and wall-forming materials (of which HSA, *viz.* human serum albumin, is one example) are described fully in WO-A-9218164 and WO-A-9608914. The materials may be water-soluble, and will generally be predominantly water-soluble, but this may not be essential. These techniques and materials, and the characteristics of the resultant microparticles described therein, are suitable for use in this invention. Thus, for example, the microparticles may be up to 50 μm, e.g. at least 1 μm, and preferably 0.5 to 5 μm in size. They can have a narrow

size range, e.g. more than 90% by mass within the desired range.

In essence, therefore, a surfactant is the additional component in known microcapsules. The amount of surfactant that is used will be chosen with primary regard to the successful formulation of the microparticles in propellant, and all the necessary parameters can be chosen by the skilled man without undue experimentation. Typically, the amount of surfactant will be 0.01 to 15%, preferably at least 0.05%, usually no more than 10%, preferably no more than 5%, and most preferably up to 2.5%, the percentages being by weight based on the weight of the drug. If too little or too much surfactant is present, formulation may be more difficult. The amount of drug in the microcapsules will be chosen with regard to ease of formulation and production, and can readily be determined by one of ordinary skill in the art. The amount of drug in the formulation for inhalation will normally be the same as has previously been used for the desired effect, e.g. up to 250 μg (or more) per actuation of a pMDI.

The following Examples illustrate the invention.

Examples

Salbutamol sulphate was chosen as a model drug substance, and microparticles were formed using three surfactants commonly used in pMDIs, i.e. lecithin, oleic acid and sorbitan trioleate. The range of surfactant to drug was from 0.05 to 5% w/w.

The current marketed pMDIs of salbutamol contain 100 μg salbutamol base equivalent per actuation. However, a typical range of dose per actuation across pMDI products covers 25-250 μg per actuation, although this can be much more. In this study, formulations were therefore prepared at 25, 125 and 250 μg per actuation, in plastic coated bottles, with HFA134a or HFA227.

These were assessed by visual examination on initial preparation and after six months storage at 20°C. In particular, differential flocculation behaviour between

differing levels of surfactant, and signs of headspace and wall drug deposition after storage, were examined.

Samples of 125 μg product with HFA134a propellant and oleic acid were also examined for priming behaviour, single shot drug delivery, fine particle dose, and expiry dosing behaviour.

Batches of microcapsules were prepared in a minispray drier. The key process parameters are given in Tables A1 (using oleic acid), A2 (using sorbitan trioleate) and A3 (lecithin).

Table A1

Total solids (% w/v)	Oleic acid (% w/w of drug)	Ethanol (% v/v)	Outlet Temp. start of run (°C)	Outlet Temp. end of run (°C)
24.1	0.05	0	66	66
24.1	0.25	0	70	70
24.2	0.5	5	63	63
24.3	1.25	5	62	60
24.6	2.5	5	65	68
24.8	3.75	10	62	64
25.1	5	15	70	75

Table A2

Total solids (% w/v)	Sorbitan Trioleate (% w/w of drug)	Ethanol (% v/v)	Outlet Temp. start of run (°C)	Outlet Temp. end of run (°C)
24.1	0.05	10	68	71
24.1	0.25	10	69	72
24.2	0.5	10	70	74
24.3	1.25	10	69	72
24.6	2.5	10	69	72
24.8	3.75	15	70	73
25.1	5	20	71	75

Table A3

Total solids (% w/v)	Lecithin (% w/w of drug)	Ethanol (% v/v)	Outlet Temp. start of run (°C)	Outlet Temp. end of run (°C)
24.1	0.05	10	66	68
24.1	0.25	10	61	65
24.2	0.5	10	68	72
24.3	1.25	10	69	71
24.6	2.5	10	77	78
24.8	3.75	15	73	73
25.1	5	15	72	76

The total solids content of the spray-drying solution ranged from 24.1-25.1% w/v, depending upon the surfactant level. To achieve solution of the higher levels of surfactant, ethanol was added to the spray-dry feedstock as a cosolvent. An inlet temperature of 140°C and a solution feed rate of 4 g per minute was employed for all batches. The feedstock was kept under nitrogen.

The prepared microcapsules were examined microscopically. From photomicrographs, the microcapsules appeared of similar size for all batches. The microcapsules were also sized using a Coulter LS, after suspension in acetone and sonication.

The mean volume median diameter of the microcapsules was 4.3 μm (range 3.8-4.8). If a smaller sized microparticle is desired, for pMDI formulation, the total solids content of the spray-dry feedstock should be reduced.

Pressurised metered dose inhalers were prepared in plastic-coated glass bottles, closed with Bespak BK357 valves, of 50 μl nominal metering volume. The appropriate weight of microcapsules was placed in the bottle (5, 25 or 50 mg for 25, 125 and 250 μg per actuation, respectively)

and 12 g HFA134a or 14.1 g HFA227 added. This gave a nominal 200 actuations per bottle.

One week after manufacture each series of bottles was shaken, then placed against a black background and allowed to settle. Photographs were taken immediately and also 1 minute, 10 minutes, 30 minutes, 20 hours and 1 week after shaking. Tables B1 and B2 give the turbidity scores after 30 minutes settling for HFA134a and HFA227, respectively. The turbidity of the samples was scored on a 0 to +++++ scale, where 0 represents a completely clear supernatant and +++++ the most turbid supernatant. The HFA134a suspensions gave a greater degree of differential settling behaviour across the series compared to HFA227 suspensions.

Table B1

Surfactant	Surfactant concentration (% w/w of drug)						
	0.05	0.1	0.5	1.25	2.5	3.75	5
Oleic acid	++++	+++	++	+++	+++++	++	+
Span 85	++++	++++	++	+++++	++	+	0
Lecithin	+++	+++	++	+++++	++++	++	++++

Table B2

Surfactant	Surfactant concentration (% w/w of drug)						
	0.05	0.1	0.5	1.25	2.5	3.75	5
Oleic acid	+++	++	++	++	++	+	++
Span 85	+++	++	+++	+++	+	++	0
Lecithin	+++	+++	+++	+++	+++	+++	+++

To have particles remaining in suspension after 30 min. is indicative of good physical stability in such systems. Turbid solutions will generally perform better.

The 125 μg salbutamol/oleic acid formulations containing 0.05, 0.5, 1.25, 2.5 and 5% w/w surfactant were examined according to the following regime:

Actuation Number	Test
1 to 8	Single actuation assay - priming data
9 to 10	Fire to waste
11 to 19	Multistage liquid impinger
15 to 95	Fire to waste
96 to 100	Single actuation assay
101 to 149	Fire to waste
150 to 159	Multistage liquid impinger
160 to exhaustion	Determine shot weight and single actuation assays to exhaustion

The actuator used in these tests was supplied by Bespak and had a jet orifice diameter of 0.53 mm.

The drug actuation and shot weight results for actuations 1 to 8 are shown in Figure 1, which is a plot of salbutamol ex-actuator (0-400 μg) against shot number (1 to 8). On the graph, ♦ represents 0.05%, ■ represents 0.5%, ▲ represents 1.25%, x represents 2.5%, and * represents 5%. As would be expected, the first actuation for each sample gave a low shot weight and corresponding low ex-actuator drug content. The samples which had shown the most turbid supernatants on visual examination (0.05% and 2.5%) displayed the most consistent dosing near to target.

The drug content per actuation has been examined for individual actuations 1 to 8 and 96 to 100. These data can be used as a measure of dose uniformity. The actuator deposition across the samples ranged from 6.4 to 34.9 μg, i.e. 5-28% of the target dose, after exclusion of actuations 1 to 3 as priming shots. As the main aim of this study was to compare different formulations, the

variability of the total dose was believed to be a better comparator.

Figure 2 is a graph of % coefficient of variation (0-60) against % oleic acid (0.05-5). Figure 3 is a graph of the range of salbutamol per actuation (0-400 μg) against % oleic acid (0.05-5). The 0.5% formulation, having the highest turbidity score, gave uniform dosing.

The size distribution of the drug emitted from the pMDI was assessed using an Astra Draco multi-stage impinger. The four stages of the impinger have cut-off diameters of 1.7, 3.1, 6.8 and 13.4 μm at 60 litre per minute air flow. The size distribution was assessed at the beginning of the pack (actuations 11 to 20) and towards the end of the pack (actuations 150 to 159). For the 0.05, 0.5, 1.25% w/w oleic acid samples, the distributions are similar at the beginning and end of the pack.

The drug per actuation for the 5.0% w/w oleic acid formulation is markedly different between the beginning and end of the pack (286 μg and 88 μg, respectively). The shape of the distributions also differs, suggesting that the drug discharged at the end of the pack is of larger size than that discharged at the start of the pack.

In a study of doses to exhaustion, the fall in shot weight was followed from actuation 160 and, after a 10% fall in shot weight was observed, the drug per actuation was determined. The results for drug per actuation through the use of the pack are shown in Figures 4 to 8.

Figures 4 to 8 are each graphs, respectively for 0.05, 0.5, 1.25, 2.5 and 5% oleic acid, of salbutamol ex-actuator (μg) against shot number. ♦ represents ex-actuator and ■ represents shot weight, in each case.

CLAIMS

1. Microparticles, up to 50 μm in size, comprising a therapeutic agent and a surfactant.

2. Microparticles according to claim 1, comprising also a wall-forming material.

3. Microparticles according to claim 1 or claim 2, whose components are at least predominantly water-soluble.

4. Microparticles according to any preceding claim, 0.5 to 10 μm in size.

5. Microparticles according to any preceding claim, obtainable by spray-drying.

6. A homogeneous formulation of microparticles according to any preceding claim and a propellant.

7. A formulation according to claim 6, wherein the propellant is a hydrofluorocarbon.

8. A metered dose inhaler comprising a formulation according to claim 6 or claim 7.

Fig.1.

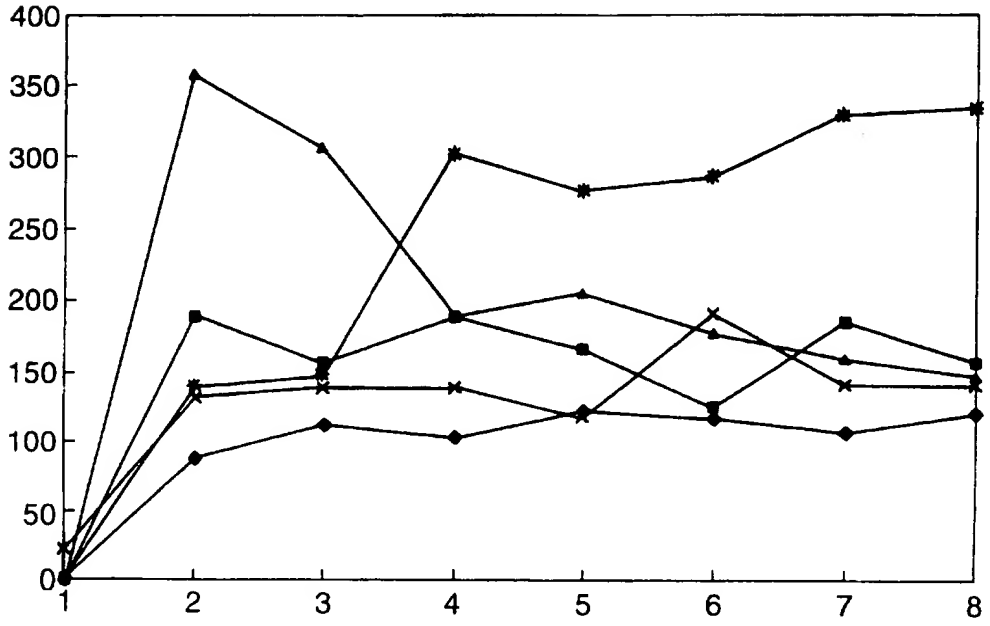
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Fig.2.

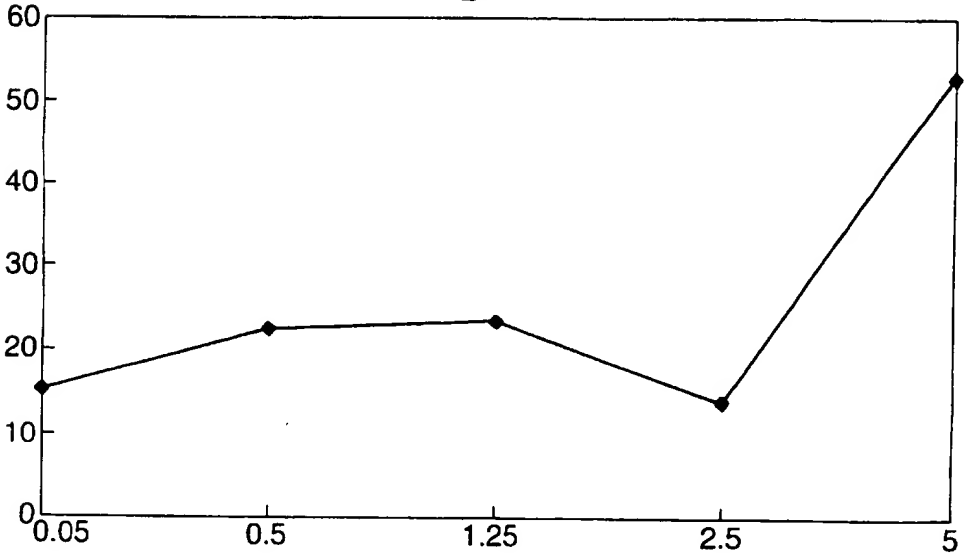
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Fig.3.

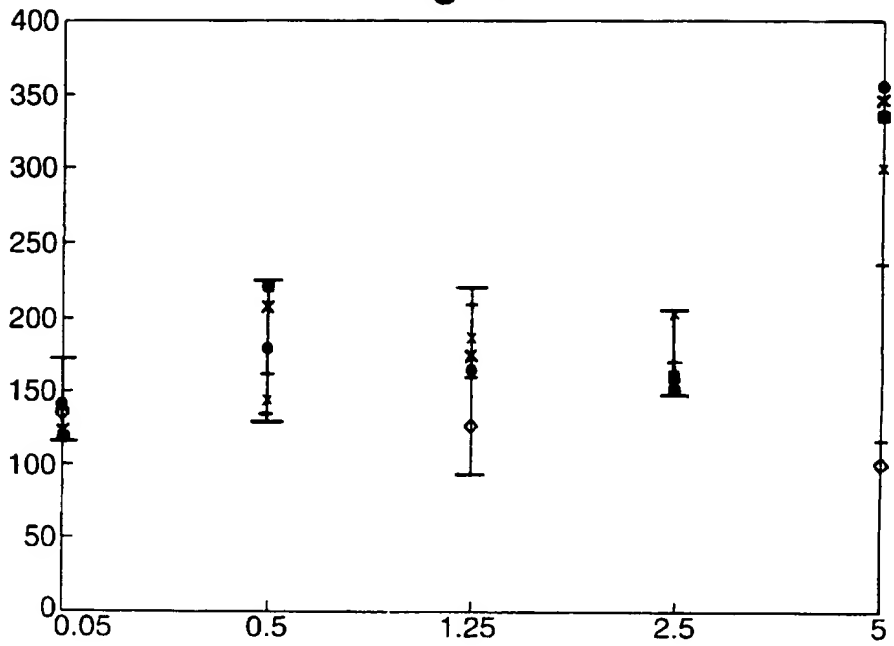
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Fig.4.

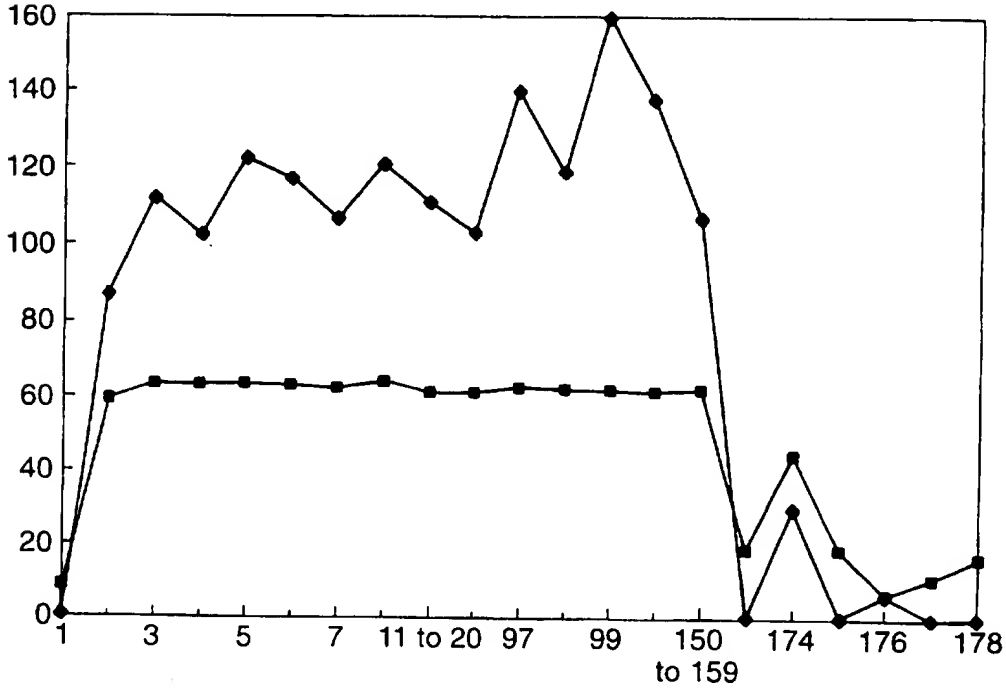
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Fig.5.

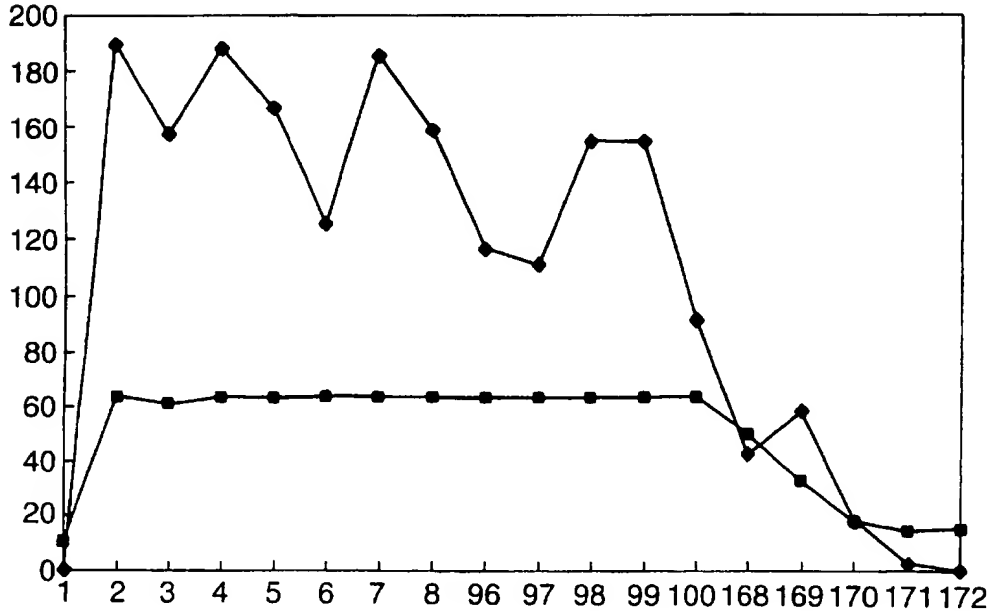
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Fig.6.

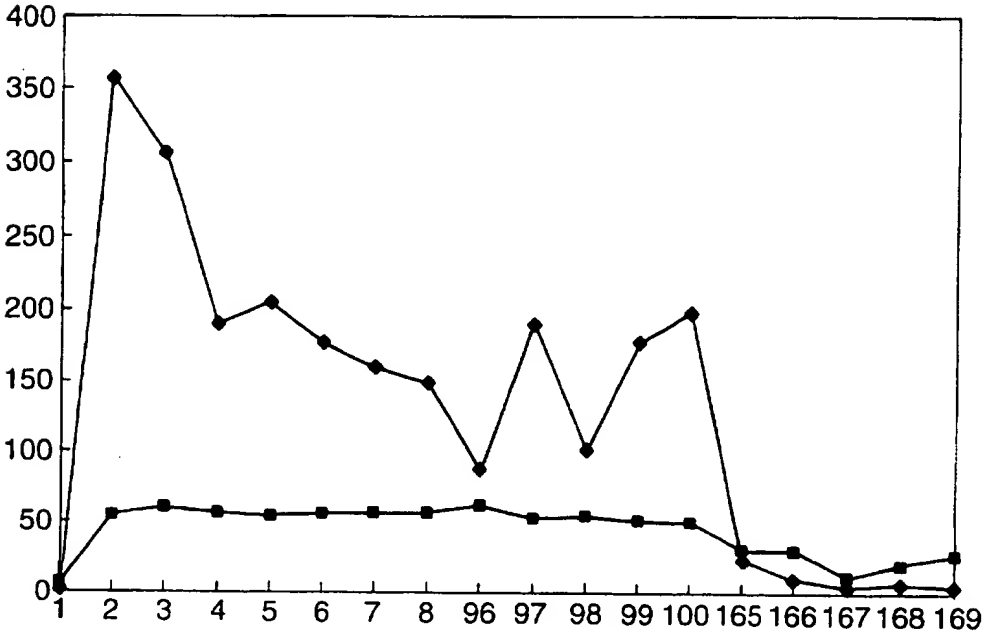
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Fig.7.

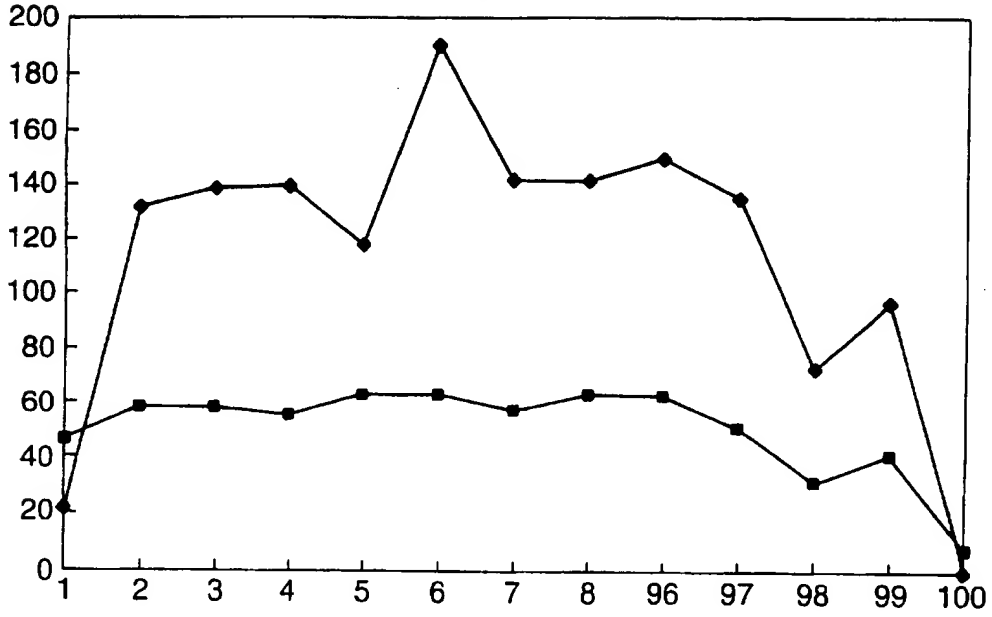
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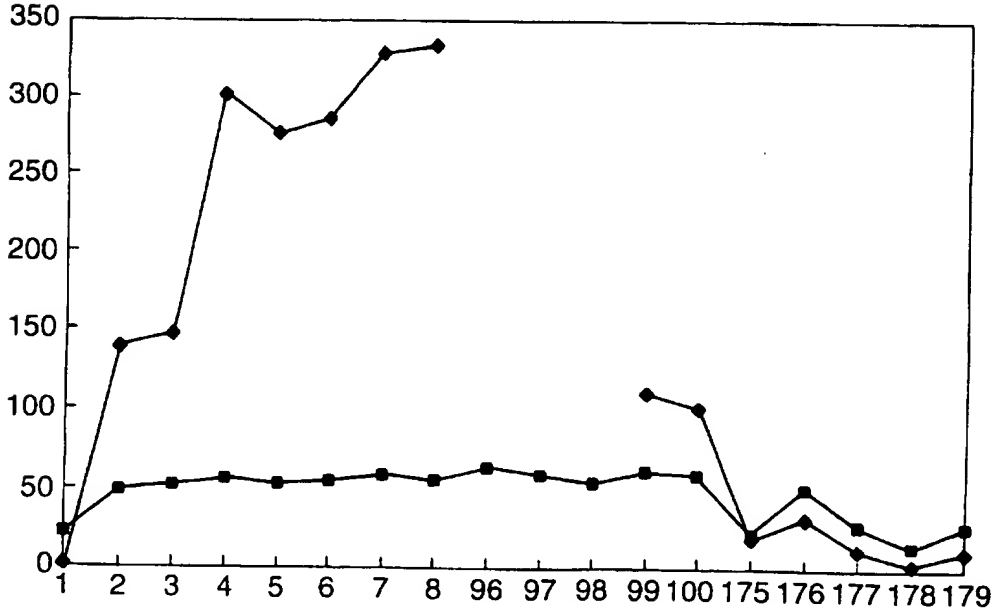
Fig.8.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INTERNATIONAL SEARCH REPORT

Inter. ial Application No
PCT/GB 97/01309

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00 A61K9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 95 27476 A (THE CENTER FOR INNOVATIVE TECHNOLOGY) 19 October 1995 see claim 1 see page 1, line 25 - page 2, line 16 see page 2, line 31 - page 3, line 1	1,4,6-8
X	EP 0 372 777 A (RIKER LABORATOIRES INC.) 13 June 1990 cited in the application see claims 1-4	1,3,4,6, 7
Y		2,5

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Date of the actual completion of the international search	Date of mailing of the international search report
25 August 1997	08.09.97

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 95 31964 A (GLAXO AUSTRALIA PTY. LIMITED ET AL.) 30 November 1995 see claims 1,2	1,4

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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